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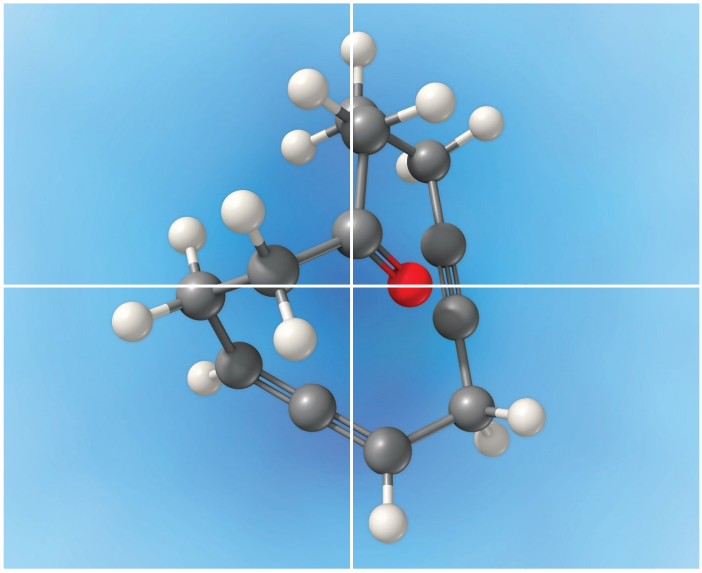

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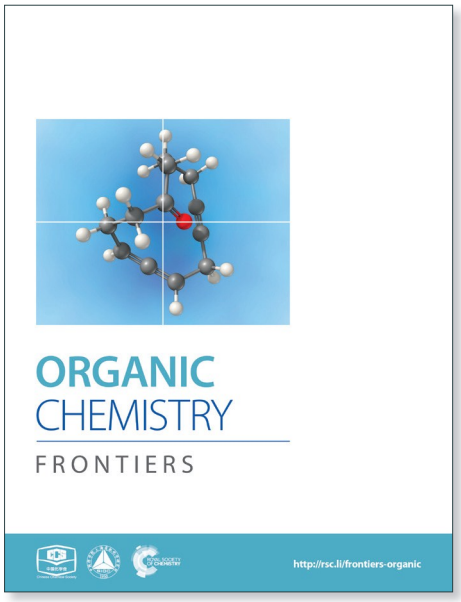

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Article

Diastereoselective and Regiodivergent Oxa-[3+2] Cycloaddition of Achmatowicz Products and Cyclic 1,3-Dicarbonyl Compounds

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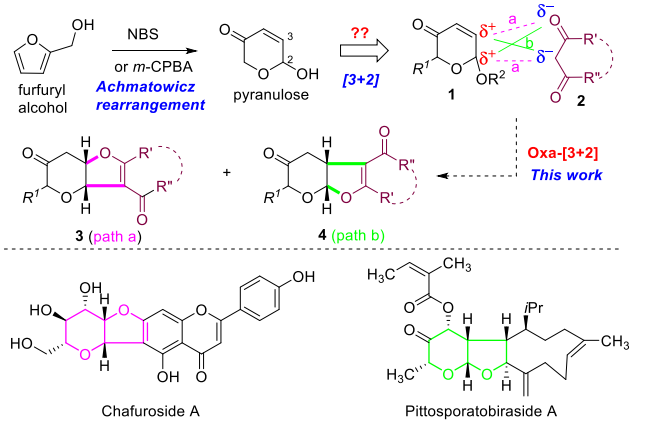
Development of two new protocols for oxa-[3+2] cycloaddition reactions of Achmatowicz products with 1,3-dicarbonyl compounds for rapid and highly efficient assembly of polycyclic furopyranones is described. Plausible mechanisms were proposed to involve either Pd-catalyzed Tsuji-Trost allylation and concomitant oxa-Michael cyclization or quinine-promoted cascade Michael addition and S_N2-type cycloacetalization.

Achmatowicz rearrangement (AchR),[1] an oxidative ring expansion process of furfuryl alcohols to pyranone acetals (also known as pyranuloses), receives growing interest in organic synthesis.[2] The expanding synthetic utility of AchR lies on the versatile reactivity of pyranuloses or their direct derivatives under different chemical conditions. For example, acylated pyranulose is a glycosyl donor for glycosylation via palladium catalysis,[3] a 1,3-dipole for [5+2] cycloaddition with alkene under basic conditions,[4] and an excellent substrate for phosphine-catalyzed [3+2]-cycloaddition with 2,3-butadienoates.[5] Our continuing interest in exploitation of AchR for natural product synthesis[6] and discovery of new reaction modes[7] prompted us to re-examine the fundamental reactivity of AchR products. On the basis of the electrophilic property at both C2 (acetal) and C3 (enone), we anticipated that the AchR product could serve as a bis-electrophile for cycloaddition reaction if the appropriate bis-nucleophile could be identified. In this regard, we fully recognized that 1,3-dicarbonyl compounds have been widely used in domino or multicomponent reactions for their intrinsic bis-nucleophilic nature.[8] Therefore, we proposed that an oxa-[3+2] cycloaddition reaction of the AchR product (or its derivative, **1**) with a 1,3-dicarbonyl compound (**2**) might occur to provide the bicyclic furopyranone (**3** or **4**), a valuable building block embodied in many natural products or bioactive compounds such as chafurosides A and B[9] and pittosporatobiraside A.[10] The inherent challenge posed by this hypothetic cyclization is the regioselectivity (path **a** versus path **b**), which has not been fully addressed although individual similar process was reported previously (path **a** by Füstner[11] with only single example and path **b** by Ramasastry[12]) under different conditions. In particular, the diastereoselectivity (if $R^1 \neq$ H) remains unexplored. Herein, we describe two new protocols for these two interesting oxa-[3+2] cycloaddition reactions, their substrate scope, and mechanistic hypothesis for rationalization of the observed regioselectivity and diastereoselectivity. In addition, an unexpected cascade involving Michael/decarboxylation/acetalization was discovered.

Scheme 1. Achmatowicz rearrangement and our hypothesis



The cyclization via path **a**[11] might involve conceptually cascade Tsuji-Trost allylation[13] and Oxa-Michael[14] cyclization while intermolecular Michael addition[15] followed by acetalization might operate in path **b**.[12] This mechanistic postulate guided us to examine the first step of the hypothetic cyclization via palladium catalysis (Tsuji-Trost allylation) or base/acid catalysis (Michael addition) since the second step

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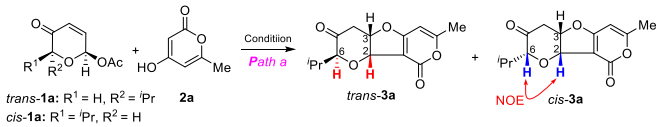
Electronic Supplementary Information (ESI) available: detailed experimental procedures, characterizations and copies of ^{1}H- and ^{13}C-NMR spectra of new compounds, and X-ray crystallographic data (*trans*-**4a**: CCDC 1444735 and *cis*-**4a**: CCDC 1444736). See DOI: 10.1039/x0xx00000x

was expected to occur concomitantly through a favourable 5-*exo*-trig or 5-*exo*-tet cyclization.[16] Therefore, we first investigated the palladium-catalyzed reaction of readily available acetoxy pyranone *trans*-**1a** (or *cis*-**1a**) and 2-pyrone **2a** (Table 1). To our delight, 1 mol% $Pd(PPh_3)_4$ was found to be effective for oxa-[3+2] cycloaddition, providing the desired *cis*-fused furopyranone *trans*-**3a** as the single diastereomer (*dr* > 30 :1) with 83% yield (entry 1). Surprisingly, the cascade cyclization of the corresponding *cis*-**1a** and **2a** delivered an inseparable mixture of *trans*-**3a** and *cis*-**3a** (*trans*/*cis* 7:10) under the identical reaction condition (entry 2). Since it is well known that Tsuji-Trost allylation with soft nucleophiles (such as 1,3-dicarbonyl compounds) typically proceeds with a net retention of stereochemistry,[17] we speculated that the poor diastereoselectivity for *cis*-**1a** might be arisen from the facile epimerization of the α chiral center of the carbonyl group in the presence of base via enol-keto tautomerization (scheme 2). To suppress this potential epimerization and gain

Table 1. Optimization of cascade cyclization via path **a** with acetoxy-2-pyranone *trans*-**1a** (or *cis*-**1a**) and 2-pyrone **2a**[a].



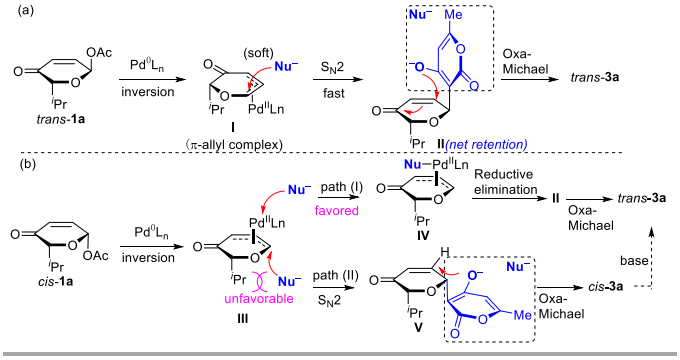
entry	substrate	Pd cat. (1 mol%)	base (1eq) /solvent	temp (°C)/ time (min)	yield[c] (%) (*trans*:*cis*)[b]
1	*trans*-**1a**	$Pd(PPh_3)_4$	Et_3N/DCM	rt/30	83 (>30:1)
2	*cis*-**1a**	$Pd(PPh_3)_4$	Et_3N/DCM	rt/30	86 (7:10)
3	*cis*-**1a**	$Pd(PPh_3)_4$	Et_3N/DCM	0/30	80 (1:10)
4	*cis*-**1a**	$Pd(PPh_3)_4$	Et_3N/DCM	-20 °C/2	10 (1:25)
5	*trans*-**1a**	$Pd(PPh_3)_4$	Et_3N/DCM	-20 °C/2	12 (>30:1)
6	*cis*-**3a**	$Pd(PPh_3)_4$	Et_3N/DCM	reflux/300	91 (>30:1)
7	*cis*-**1a**	$Pd(PPh_3)_4$	Et_3N/DMF	rt/30	85 (8:1)
8	*cis*-**1a**	$Pd(PPh_3)_4$	Et_3N/THF	rt/30	60 (1:1)
9	***cis*-1a**	**$Pd(PPh_3)_4$**	**Et_3N/Tol**	**rt/30**	**90 (>30:1)**
10	*cis*-**1a**	$Pd(OAc)_2$	Et_3N /Tol	rt/30	59 (>30:1)
11	*cis*-**1a**	$PdCl_2$	Et_3N /Tol	rt/30	8 (>30:1)
12	*cis*-**1a**	$Pd_2(dba)_3$	Et_3N /Tol	rt/30	35 (>30:1)
13	*cis*-**1a**	$Pd(PPh_3)_4$	DBU/Tol	rt/30	85 (>30:1)
14	*cis*-**1a**	$Pd(PPh_3)_4$	Quinine/Tol	rt/30	89 (>30:1)
15	***trans*-1a**	**$Pd(PPh_3)_4$**	**Et_3N/Tol**	**rt/30**	**92 (>30:1)**

Notes: a: the reaction was run with 0.1 mmol of **1a**. b: ratio was determined by NMR analysis of the crude reaction mixture. c: combined yield after flash column chromatography on silica gel. DMF: N,N-dimethylformamide; THF, tetrahydrofuran; DCM: dichloromethane; Tol: toluene; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene.

mechanistic insights into this unusual stereochemistry-dependent diastereoselectivity, we carried out the oxa-[3+2] cycloaddition reaction at variable temperature and time (entries 3-6). Apparently, at lower reaction temperature (0 °C or −20 °C) and within shorter reaction time (quenching the reaction within 2 minutes) the reaction of *cis*-**1a** or *trans*-**1a** with **2a** proceeded with the expected retention of configuration and provided the corresponding products *cis*-**3a** and *trans*-**3a**, respectively, with excellent diastereoselectivity but low conversion. When *cis*-**3a** was subjected to the heating condition (entry 6), *trans*-**3a** was obtained exclusively (*dr* > 30:1) with 91% yield, which suggested *trans*-**3a** was the thermodynamically more stable product. This finding prompted us to search a mild condition that could exclusively produce *trans*-**3a** from both *cis*-**1a** and *trans*-**1a**. Preliminary screenings of solvents (entries 7–9: DMF, THF and toluene), bases (entries12–14: DBU, quinine and Et_3N) and palladium catalysts [entries 9–12: $Pd(PPh_3)_4$, $PdCl_2$, $Pd_2(dba)_3$ and $Pd(OAc)_2$] led us to identify the optimal condition for both substrates (entries 9 and 15): triethyl amine (1 eq) as the base, $Pd(PPh_3)_4$ (1 mol%) as the catalyst and toluene as the solvent at room temperature for 30 mins, which afforded *trans*-**3a** with an excellent yield (90% from *cis*-**1a**, 92% from *trans*-**1a**) and diastereoselectivity (*trans*-**3a**, *dr* > 30:1). The structures for *cis*-**3a** and *trans*-**3a** were confirmed by careful analysis of spectral data (*cis*-fused furopyranone with a distinctive high value of *J* = 8 Hz and the nOe observed at H2 and H6).

On the basis of these results (Table 1), we proposed plausible mechanistic pathways for the oxa-[3+2] cycloaddition reaction (Scheme 2). The reaction of *trans*-**1a** and **2a** (Nu^-) was initiated by oxidative addition of palladium followed by a S_N2-type nucleophilic substitution and subsequent intramolecular oxa-Michael cyclization (Scheme 2a). The oxa-[3+2] cycloaddition reaction of *cis*-**1a** with **2a** involved the similar oxidative addition of palladium and oxa-Michael cyclization, but it might operate differently in the course of substitution through path (I), probably due to the unfavourable steric interaction of the isopropyl group with the incoming nucleophile (**2a**). In path (I) the nucleophilic substitution occurs at the palladium followed by reductive elimination (**III** → **IV** → **II**), which resulted in a net inversion of stereochemistry.[17] However, the reaction temperature and solvent (*e.g.,* THF) might make path (II) being a competitive pathway as shown in Table 1. It is less likely that epimerization of *cis*-**3a** to *trans*-**3a** occurred through enol-keto tautomerization under the mild reaction condition within short time because subjection of a mixture of *cis*-**3a** and *trans*-**3a** (*cis*/*trans* = 5/4) to the standard reaction condition resulted in small increase of the ratio of *trans*-**3a** (*cis*/*trans* 3/7).

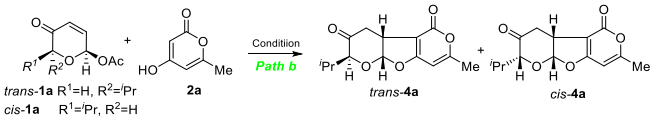
Scheme 2. Proposed mechanism of cascade Tsuji-Trost allylation and Oxa-Michael cyclization.



Next, we turned our attention to explore the possibility of an oxa-[3+2] cycloaddition reaction via path **b** involving intermolecular Michael addition and concomitant Acetalization

under non-aqueous conditions (different from Ramasastry's condition). We first investigated the reaction of *trans*-**1a** and **2a** (Table 2). Fortunately, treatment of *trans*-**1a** and **2a** with triethyl amine in DCM at reflux for 12 h provided the expected *cis*-fused furopyranone *cis*-**4a** in 60% yield with excellent diastereoselectivity (*dr* = 15:1). Encouraged by this result, we began to examine different bases (entries 1–7 and 14–15) and solvents (entries 16–18) in order to identify the optimal reaction condition (Table 2). It was found that in the presence of one equivalent of quinine[18] (entry 8) the reaction proceeded cleanly and gave the best yield and stereoselectivity, which was in contrast to the inorganic base (entries 14 and 15) that could not promote the cycloaddition reaction. Interestingly, extended reaction time and/or increased reaction temperature resulted in isomerization of *cis*-**4a** to *trans*-**4a** (entry 8–10). However, similar isomerization was not observed in the oxa-[3+2] cycloaddition reaction of *cis*-**1a** and **2a** under the identical condition via path b, which led to exclusive formation of *trans*-**4a** (entry 11–13). These seemingly contradictory results might be attributed to

Table 2. Optimization of cascade reaction via path **b** with acetoxy-2-pyranone *trans*-**1a** (or *cis*-**1a**) and 2-pyrone **2a**[a].

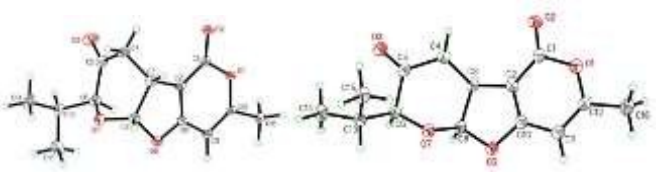


entry	substrate	base (1 eq)	solvent	temp (°C) /time (h)	yield[c] (%) (*trans*:*cis*)[b]
1	*trans*-**1a**	Et_3N	DCM	reflux/12	60 (1:15)
2	*trans*-**1a**	DBU	DCM	reflux/12	53 (1:15)
3	*trans*-**1a**	$(^iPr)_2NEt$	DCM	reflux/12	75 (1:1)
4	*trans*-**1a**	DABCO	DCM	reflux/12	70 (1:10)
5	*trans*-**1a**	pyridine	DCM	reflux/12	NR
6	*trans*-**1a**	pyrrolidine	DCM	reflux/12	NR
7	*trans*-**1a**	DMAP	DCM	reflux/12	75 (1:1)
8	***trans*-1a**	**quinine**	**DCM**	**reflux/12**	**90 (1:15)**
9	*trans*-**1a**	quinine	DCM	reflux/24	88 (1:10)
10	*trans*-**1a**	quinine	DCM	reflux/36[d]	85 (>30:1)
11	*cis*-**1a**	quinine	DCM	rt/5	21 (>30:1)
12	*cis*-**1a**	quinine	DCM	rt/12	49 (>30:1)
13	***cis*-1a**	**quinine**	**DCM**	**reflux /12**	**91 (>30:1)**
14	*trans*-**1a**	$NaHCO_3$	DCM	reflux/12	NR
15	*trans*-**1a**	NaOH	DCM	reflux/12	NR
16	*trans*-**1a**	quinine	Tol	50 °C/12	80 (3:1)
17	*trans*-**1a**	quinine	THF	50 °C/12	75 (1:3)
18	*trans*-**1a**	quinine	MeOH	rt/12	trace
19	*trans*-**1a**	$NaHCO_3$ (2 eq)	H_2O	rt/1	25 (3:1)

Notes: a: the reaction was run with 0.1 mmol of **1a**. b: ratio was determined by NMR analysis of the crude reaction mixture. c: combined yield after flash column chromatography on silica gel. d: the reaction was performed in tube sealing at 70 °C for 36 h in DCM. TFA: trifluoroacetic acid. DABCO: triethylenediamine; DMAP: 4-dimethylaminopyridine.

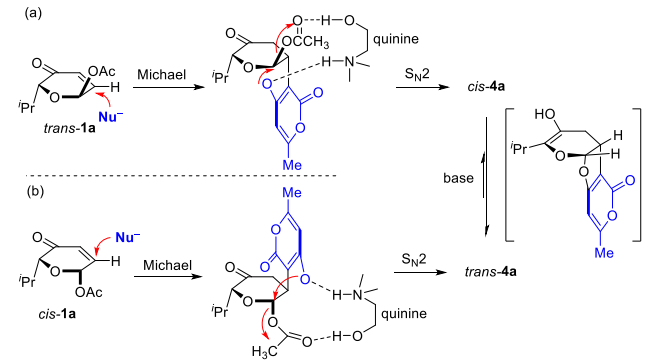
formation of the thermodynamically more stable *trans*-**4a** through the enol-keto tautomerization in the presence of base at reflux (scheme 3). The structures of *cis*-**4a** and *trans*-**4a** were unambiguously substantiated by single crystal X-ray diffraction analysis (Figure 1). Notably, the reaction of *trans*-**1a** and **2a** under previously reported condition[12] (entry 19) was very sluggish (25% conversion at rt for 12h) with poor diastereoselectivity (dr 3:1), which was in sharp contrast to the reported observation ($NaHCO_3$, H_2O, rt, 1h, 88%).[12]

Figure 1. ORTEP Diagrams of *trans*-**4a** and *cis*-**4a**.



Mechanistically, we speculated that the oxa-[3+2] cycloaddition reaction started with Michael addition,[19] which diastereoselectivity was controlled by the acetoxy group to avoid otherwise steric interaction developed between the acetoxy group and the incoming nucleophile. The second step of the cascade sequence might involve transacetalization[20] through an intramolecular S_N2 substitution, which under the basic condition using CH_2Cl_2 as the aprotic solvent was promoted by dual activation[21] through double hydrogen bonding interactions with quinine.[22] Although transacetalization via the S_N1 substitution (via oxonium ion)[23] could not be ruled out and more experimental work needed to further elucidate the detailed mechanism, we choose at this stage to further expand the substrate scope of these two novel oxa-[3+2] cycloaddition reactions.

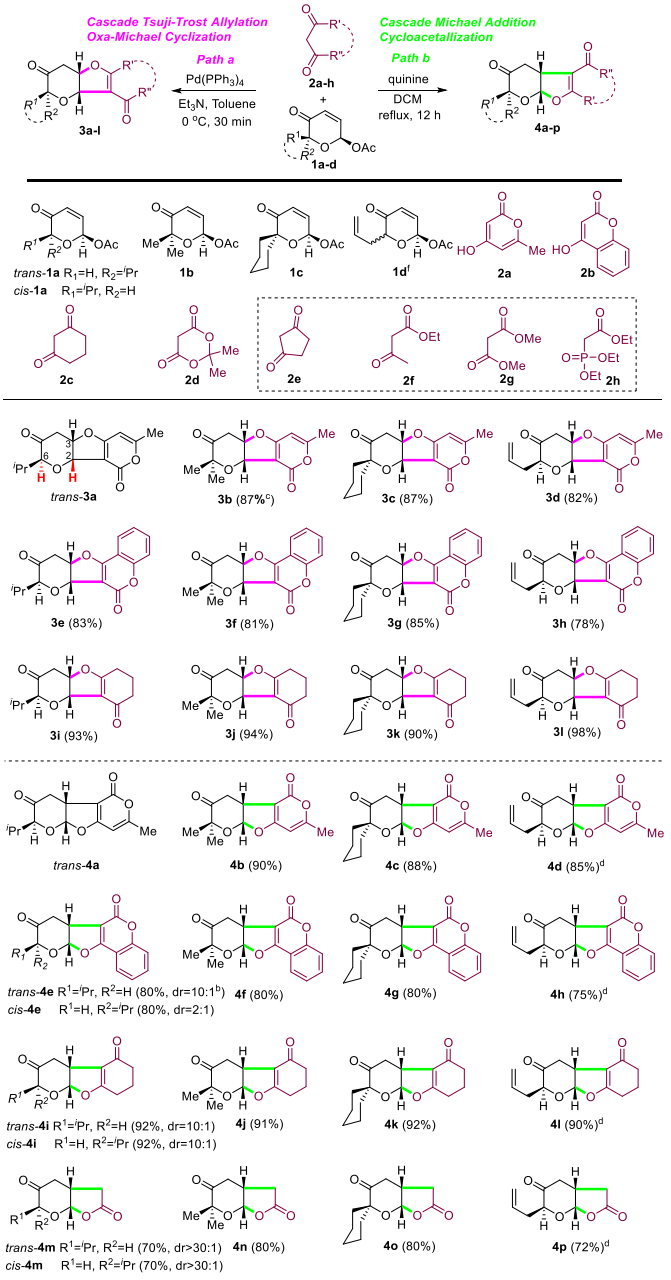
Scheme 3. Proposed mechanism of cascade Michael addition and acetalization.



With the optimized conditions in hand, the scope and limitations of both oxa-[3+2] cycloaddition reactions (path **a** versus path **b**) were examined with a small set of acetoxy-2-pyranone **1a**–**d** and a series of 1,3-dicarbonyl compounds (**2a**–**h**) (Table 3). In general, both oxa-[3+2] cycloaddition reactions of acetoxy-2-pyranones with different substitutions at C6 (**1a**–**d**) and most six-membered cyclic 1,3-dicarbonyl compounds (**2a**–**d**)[24] could proceed smoothly under our optimized conditions to provide the desired furopyranones (**3b**–**l** and **4b**–**p**) in good to excellent yield (72-98%) with excellent diastereoselectivity (*dr* ≥ 10:1). Unexpectedly, 1,3-cyclopentanedione (**2e**), acyclic 1,3-dicarbonyl compounds

(*e.g.,* **2f** and **2g**) and triethyl phosphonoacetate (**2h**) did not react with any acetoxy-2-pyranones (**2a–d**) under various conditions, which could not be well rationalized at this point. It was noteworthy that a mixture of diastereomeric acetoxypyranone **1d** could be employed for both oxa-[3+2] cycloaddition reactions to provide the corresponding cyclization products as the single diastereomer with excellent yields (**3d**, **3h**, **3l**, **4d**, **4h**, **4l**, **4p**). Interestingly, the reaction of acetoxy-2-pyranones with Meldrum's acid[25] (**2d**) under our quinine-mediated reaction condition delivered the unexpected decarboxylation products (**4m**–**n**) in excellent yields, while Meldrum's acid was not reactive towards acetoxy-2-pyranones with palladium catalysis. Further exploration of this finding is ongoing and will be reported in due course.

Table 3. Scope for cascade reaction of acetoxy-2-pyranone **1a**-**d** and 1,3-dicarbonyl compounds **2a**-**d**[a]



Notes: a: the reaction was run with 0.1 mmol of **1a**-**d**; b: ratio was determined by NMR analysis of the crude reaction mixture; c: combined yield after flash column chromatography on silica gel; d: all cascade reaction of **1d** and **2a**-**d** was carried out in tube sealing at 70 °C for 36 h in DCM; f: the allylic substrate is a mixture of diastereomers (*tran*:*cis*=3:2).

Conclusions

In summary, we have developed two new protocols for oxa-[3+2] cycloaddition reactions, which allowed a rapid and highly efficient assembly of structurally interesting polycyclic furopyranones. Importantly, we have demonstrated for the first time that Achmatowicz products could be employed as bis-electrophiles for diastereoselective and regiodivergent oxa-[3+2] cycloaddition reactions with 1,3-dicarbonyl compounds, which greatly expands the synthetic utility of Achmatowicz rearrangement. Plausible mechanistic pathways for both oxa-[3+2] cycloaddition reactions were proposed on the basis of our new results and findings to rationalize the regiodivergence and diastereoselectivity: palladium catalysis involves Tsuji-Trost allylation followed by intramolecular oxa-Michael cyclization; quinine-mediated cascade cyclization occurs through a diastereoselective intermolecular Michael addition and a subsequent S_N2-type cycloacetalization by dual activation. In addition, we discovered an unexpected new cascade sequence: Michael addition/decarboxylation/acetalization. These two novel oxa-[3+2] cycloaddition reactions may find applications in drug discovery and natural product synthesis.

Acknowledgements

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